Chemical Strategies for Activating PINK1, a Protein Kinase Mutated in Parkinson's Disease

Olivia A. Lambourne,[a] and Youcef Mehellou*[a]

PINK1 is a ubiquitously expressed mitochondrial serine/threonine protein kinase that has emerged as a key player in mitochondrial quality control. This protein kinase came to prominence in mid-2000s, when PINK1 mutations were found to be causative of early-onset Parkinson's disease (PD). As most of these PD-related mutations occurred in the kinase domain and impaired PINK1 catalytic activity, it was suggested that small molecules that activate PINK1 would maintain mitochondrial quality control and as a result offer advantageous neuroprotective effects. Working on this hypothesis, few small molecule PINK1 activators, which offered critical insights and distinct approaches for activating PINK1, have to date been discovered. Herein, we briefly highlight the discovery of these small molecules and offer a future insight into the development of small molecule PINK1 activators as potential treatments for PD.

The discovery of PTEN-induced kinase 1 (PINK1) mutations as causative of early-onset PD in 2004[1] represents a landmark finding in the field of PD. This is because it provided the first direct evidence of mitochondrial dysfunction having a primary role in the development of PD. PINK1 is a unique protein kinase as it has an *N*-terminal mitochondrial targeting domain and three insertion loops within its catalytic kinase domain.[2] Back then, the molecular mechanism by which PINK1 mutations contributed to the development of PD was unclear. However, a series of fundamental discoveries have since been made, which provided a clearer understanding of how PINK1 mutations cause PD.[3] Interestingly, most of the PINK1 mutations identified to date, fall within the kinase domain and abolish its catalytic activity.[4] Indeed, all of the seventeen human PD PINK1 missense mutations studied were found to have suppressed or completely depleted kinase activity in vitro compared to the wild-type PINK1 kinase.[4] This finding indicated that restoring or maintaining PINK1 kinase activity could pose as a potential therapeutic strategy for PD. This hypothesis was supported by subsequent studies that indicated that the loss of PINK1 resulted in stress-induced mitochondrial dysfunction and neuronal apoptosis in many mammalian cells including neuronal cells, a phenomenon that was rescued by the overexpression of PINK1 wild-type.[5] Furthermore, the kinase activity of PINK1 was also noted in Drosophila models as being critical for the mitochondrial translocation of its E3 ubiquitin ligase substrate, parkin,[6] a key process in the eventual repair or removal of damaged mitochondria.

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At the molecular level, PINK1 is recruited to the mitochondria via its *N*-terminal mitochondrial targeting domain, which is then cleaved off allowing a truncated version of PINK1 to dissociate from the mitochondria. This short version of PINK1 is then rapidly degraded via the N-end rule pathway and ubiquitin–proteasome system.[7] However, in damaged mitochondria, where there is a loss of the mitochondrial membrane potential ($\Delta\psi m$), PINK1 associates with the translocase of the outer membrane (TOM) on the outer mitochondrial membrane (OMM) allowing it to homodimerize, autophosphorylate and as a result become catalytically active.[8] Subsequently, active PINK1 phosphorylates parkin, which is also mutated in early-onset PD,[9] at serine 65 (Ser65) and ubiquitin also at Ser65.[3b, 3c, 3h, 3j] This leads to the activation of parkin and the ubiquitylation of a series of OMM proteins.[8, 10] This eventually results in the recruitment of ubiquitin adaptor proteins and the engulfment of the damaged mitochondria by autophagosomes, a process termed mitophagy, which recycles the damaged mitochondria (**Figure 1**).[3k]

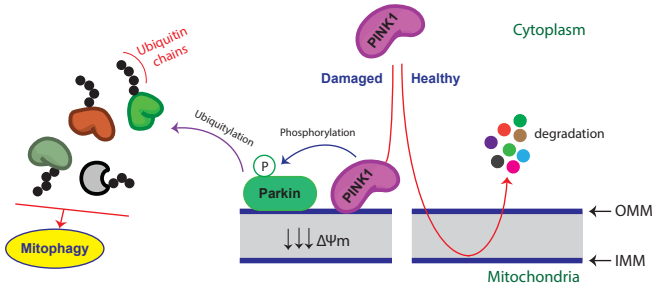

Figure 1. PINK1-signalling in healthy and damaged mitochondria. Under resting conditions, healthy mitochondria, PINK1 is recruited to the outer mitochondrial membrane (OMM) and degraded. However, when the mitochondria is damaged (↓↓↓ $\Delta\psi m$), PINK1 is stabilized on the OMM where it phosphorylates parkin at Ser65 and ubiquitin at Ser65, a process that induces mitophagy and results in the recycling of damaged mitochondria.

Although in vivo studies into PINK1-related mitophagy have been scarce, a recent report indicated the level of neuronal basal mitophagy in PINK1 knock out mice was comparable to the wild-type.[11] This observation should be taken with caution as PINK1 knockout mice do not show Parkinson-like symptoms[12] and the PINK/Parkin signaling pathway was not stimulated in this in vivo study. Nevertheless, mitophagy is still well-supported as a protective mechanism that avoids the toxic accumulation of damaged or excess mitochondria in cells and consequently oxidative damage and cell death.[13] Together, these discoveries imply that PINK1 may act as a master regulator of mitochondrial quality control within neurons and hence provided a direct link between PINK1 activity and neurodegeneration.

Working on the hypothesis that PINK1 activation would have beneficial neuroprotective effect that could slow down the progression of Parkinson's disease, some attempts at discovering small molecule PINK1 activators have been reported as discussed below.

Small molecule PINK1 activators

To date, only few small-molecule PINK1 activators have been identified and these could be classified into two groups depending on their mechanism of action. These are direct activators, which are believed to act on PINK1 directly, and indirect activators, which do not act directly on PINK1 to produce their effects.

1. Direct PINK1 activators

This first discovery of a direct small molecule PINK1 activator was made by the Shokat lab in 2013 when they reported that kinetin riboside triphosphate (KTP) acts as an ATP neo-substrate and activates PINK1 in vitro and in cells.[14] This was a result of the finding that kinetin riboside triphosphate with a gamma thiophosphate (KTPγS) was used as an ATP neo-substrate by the recombinant PINK1 WT kinase domain and its G309D mutant with a better efficiency than the natural substrate ATP in vitro.[14] Encouragingly, analysis of this in vitro reaction products indicated that the PINK1 kinase domain as well as the PINK1 peptide substrate used in this assay had a thiophosphate group incorporated.[14] This confirmed the ability of PINK1 to use KTPγS as a neo-substrate to autophosphorylate and also subsequently phosphorylate its substrates.[14] Notably, a selection of other N^6-substituted adenosines triphosphates, e.g. N^6-benzyl adenosine triphosphate, were unable to activate PINK1 in vitro.[14] In cells, it was shown that the KTP precursor kinetin underwent four consecutive metabolic (activation) steps, one glycosylation and three phosphorylation bioconversions, to generate the active KTP metabolite (**4**, **Figure 2A**), which acted as a PINK1 ATP-neo-substrate.[14] Indeed, in cells treated with kinetin, KTP was detected and a degree of PINK1 activation was also observed as judged by increased phosphorylation of the anti-apoptotic protein Bcl-xL, a PINK1 substrate.[14] Although subsequent work showed that long-term oral dosing of kinetin did not protect against α-synuclein-induced neurodegeneration in rodent models of PD,[15] it must be noted that kinetin itself is of very low efficacy in cells[14] and no studies as of yet have reported on the brain uptake of the nucleobase kinetin.

To generate more potent PINK1 activators, we hypothesized that working at the nucleoside monophosphate level, i.e. kinetin riboside monophosphate (**3**, **Figure 2**), would by-pass the glycosylation and first phosphorylation steps, which if they do not proceed with high efficiency in cells and in vivo, would limit the amounts of active KTP generated. However, it is well established that nucleoside analogues monophosphates have poor cellular uptake. This is because of their incompatibility with membrane nucleoside transporters, extracellular dephosphorylation to generate the parent nucleoside and their polar (negatively charged) nature at physiological pH (< 7.4), which limits their passive diffusion across cell membranes.[16] To overcome these challenges, a number of monophosphate prodrug approaches have been developed (see Hecker and Erion,[16b] Wiemer and Wiemer[17]) and these have been used widely in the discovery of nucleotide-based therapeutics.[18] Among the most successful monophosphate prodrug approaches is the ProTide technology,[19] which to date has delivered over ten clinical candidates and two FDA-approved drugs.[20] In this prodrug approach, the monophosphate group is masked by an aryl group and an amino acid ester generating a prodrug that is neutral at physiological pH and is passively taken up by cells (**Figure 2B**).[19] Upon cell entry, the masking groups are enzymatically cleaved off to release the nucleoside analogue monophosphate, which could then be further phosphorylated by cellular nucleotide kinases to the active triphosphate species (**Figure 2B**).[19]

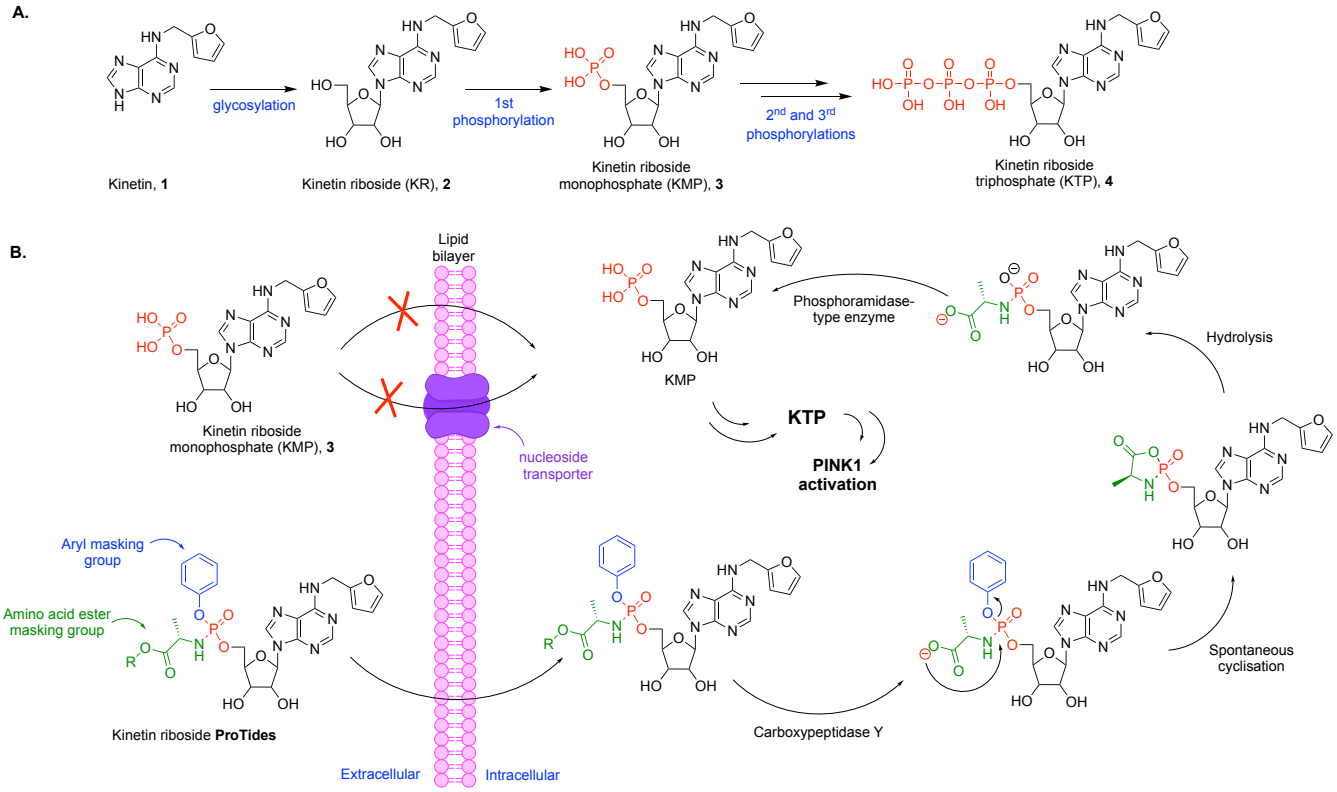

Figure 2. Nucleobase, nucleoside and ProTide activators of PINK1. **A**. Chemnical structure of kinetin and ist metabolites leading tot he genration oft he active PINK1 ATP-neosubstrate KTP. **B**. Cellular uptake and postulated metabolism of kinetin riboside ProTides. R = methyl, isopropyl, *tert* butyl and benzyl.

Encouraged by the success of the ProTide technology in discovering nucleotide-based therapeutics, we applied this prodrug approach to kinetin riboside monophosphate, KMP.[21] Four KMP ProTides were synthesized with varying esters (methyl, isopropyl, *tert*butyl and benzyl). These were shown to be stable in human serum for >12 h and were metabolized in vitro by carboxypeptidase Y to generate the desired nucleotide metabolite. When studied for their ability to activate PINK1 in HEK293 cells stably overexpressing PINK1 and transiently transfected with parkin, these ProTide prodrug showed far superior activation of PINK1 compared to the parent nucleobase kinetin.[21] This was judged by parkin Ser65 phosphorylation after treatment with different concentrations of KMP ProTides. Interestingly, the nucleoside kinetin riboside was also able to activate PINK1 in cells to a level comparable to that observed with the most potent KMP ProTide.[21] This suggested that the glycosylation of kinetin into kinetin riboside rather than the first phosphorylation step may be the rate-limiting step in the four bioconversion steps of kinetin into its active KTP. The data from this study confirmed the initial observation of kinetin being a weak activator on PINK1 in cells and this may explain the lack of in vivo PINK1 activation using kinetin.[15] Additionally, it supported our hypothesis that for unnatural (modified) nucleobases such as kinetin, their multi-step bioconversion in cells and in vivo may not be as efficient as for natural nucleobases and this ultimately limits their pharmacological efficacy. Overall, this work highlighted that working on the nucleoside or the nucleoside monophosphate levels could yield more potent activators for PINK1 than the use of nucleobases.

2. Indirect PINK1 activator

As mentioned above, the loss of the mitochondrial membrane potential leads to the activation of PINK1.[3b] Inspired by this observation, a number of compounds that are known to disrupt mitochondrial function have been identified as promising PINK1 activators. Among these are the proton ionophores carbonyl cyanide *m*-chlorophenyl hydrazone (CCCP) and carbonyl cyanide-4-(trifluoromethoxy)phenylhydrazone (FCCP) as well as the potassium uniporter valinomycin.[3b, 8] Interestingly, unlike CCCP and FCCP, valinomycin was able to depolarize the mitochondrial membrane potential without affecting the pH gradient indicating that PINK1 is specifically activated by loss of the mitochondrial membrane potential ($\Delta\psi$m). Despite the promise of these agents in activating PINK1, their cellular toxicity has hindered their in vivo investigations and their possible development as potential small molecule PINK1 activators. Keen on discovering safe small molecules that could manipulate mitochondrial membrane potential and thus activate PINK1, we focused our attention niclosamide (**Figure 3**), a clinical agent that has been reported in numerous studies to uncouple mitochondrial membrane potential.[22] Niclosamide is an anthelminthic drug used for decades to treat tapeworm infections[23] and it has an encouraging safety profile in vivo.[22b, 24]

Treatment of parkin-overexpressing HeLa cells, which express PINK1 endogenously, with niclosamide led to potent activation of PINK1 EC_{50} in cells as judged by parkin phosphorylation at Ser65. Additionally, in niclosamide treated cells CISD1, a substrate of parkin,[25] was ubiquitylated in a niclosamide dose-dependent manner indicating the activation of the PINK1 and parkin. Notably, this PINK1 downstream signaling, namely parkin S65 phosphorylation and CISD1 ubiquitylation, was abolished in PINK1 KO cells treated with niclosamide. In vitro kinase assays indicated that niclosamide was not able to activate recombinant PINK1 suggesting that niclosamide is an indirect activator of this kinase. This observation was supported by data from cell assays showing the cleavage of full length OPA1[26] protein because of mitochondrial membrane depolarization in wild-type as well as PINK1 KO cells treated with niclosamide. Given the simple chemical structure of niclosamide, three of its derivatives (**Figure 3**) were synthesized and only one of these, AM85, showed PINK1 activation comparable to niclosamide. Encouragingly, niclosamide and AM85 activation of PINK1 was not limited to cell studies as it was also observed in cultured neurons.[25]

Studies into understanding how niclosamide and AM85 activated PINK1 indicated that they both induced mitochondrial membrane uncoupling, a phenomenon known to activate PINK1.[3b, 25] Intriguingly, the mitochondrial membrane uncoupling effect caused by niclosamide and AM85 was reversible and did not cause permeant damage to the mitochondrial membrane potential.[25]

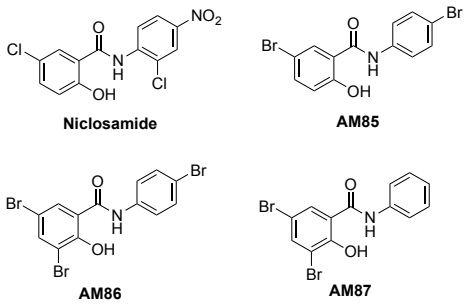

Figure 3. Chemical structures of niclosamide and its analogues that have been studied for PINK1 activation.

Despite the promise of niclosamide as a PINK1 activator, it has a number of limitations that hinder its possible repurposing for the treatment of PD. First, niclosamide is a promiscuous compound since it manipulates many signaling pathways in cells and in vivo.[23] Deconvoluting the niclosamide-mediated PINK1 activation mechanism from the other non-PINK1 related effects, albeit it a challenge, would be extremely informative and would facilitate the discovery of more specific PINK1 activators. Second, as a drug molecule, niclosamide has poor drug-like properties that include poor solubility and inefficient absorption. Thus, in many studies, niclosamide prodrugs with improved drug-like properties have been used.[22b, 27] However, to date, these niclosamide prodrugs have been studied in non-central nervous system conditions and therefore their brain-penetration properties are unknow.

Future Outlook

Given the direct genetic link between PINK1 mutations and PD, it is of no surprise to see an increased pursuit of the discovery of PINK1 activators as potential PD treatments. Although this pursuit is yet to deliver compounds with drug-like properties that support their in vivo studies, there is no doubt that the PINK1 activators discussed in this Highlight have confirmed the amenability of PINK1 to be activated by small molecules and both classes of PINK1 activators, direct and indirect, may have the potential to treat PD in the future. The immediate step from these early discovery studies is the optimisation of these compounds to generate potent, safe and brain-penetrant PINK1 activators. This may be a relatively easier challenge for direct PINK1 activators as compared to the indirect ones, whose exact molecular target is yet to be identified. It is also worth noting that for indirect PINK1 activators, especially those that operate by depolarizing the

mitochondrial membrane, their safety in vivo needs to be established prior to extensive in vivo studies and progression in the pre-clinical development pipeline. Ultimately, the challenge for PINK1 activators will be whether they exhibit PINK1 activation in vivo that is sufficient to induce meaningful neuroprotective effects and hence offer hope in treating PD. Notably, with some reports linking PINK1 and its mutations to sporadic PD,[28] PINK1 activators may have a wider use in treating this disease than initially thought.

Overall, the highlighted potential of small molecule PINK1 activators as well as the remaining PINK1-related unanswered questions show that this field is still at its early stages and there is a lot more to be discovered over the next few years. Together, this makes the discovery of small molecule PINK1 activators scientifically exciting and will inform and influence the discovery and development of new PD therapeutics.

Keywords: PINK1 • Parkinson's • Disease • Activation • Kinase

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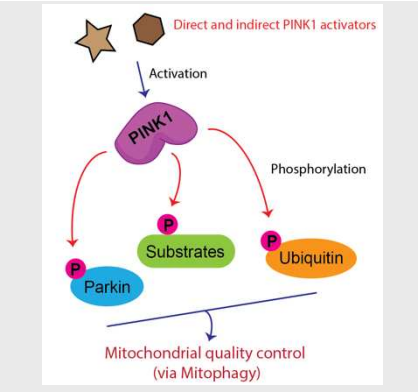
Entry for the Table of Contents

HIGHLIGHT

PINK1 is a serine/threonine protein kinase mutated in early-onset Parkinson's disease (PD). As most of the PINK1-causing mutations are loss of function mutations, PINK1 activation emerged as potential approach for slowing down neurodegeneration. Herein, recent efforts in discovering small molecule PINK1 activators as well as a brief outlook on their future development as potential PD treatments is provided.



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